EXHIBIT 23

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Docket No.: BBI-093CPDV
(PATENT)

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Patent Application of:
Jochen G. Salfeld *et al.*

Application No.: 10/884,830 Confirmation No.: 5175

Filed: July 1, 2004 Art Unit: 1646

For: HUMAN ANTIBODIES THAT BIND HUMAN IL-12 AND METHODS FOR PRODUCING Examiner: Bruce D. Hissong

MS Amendment
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

AMENDMENT AND RESPONSE TO OFFICE ACTION

Dear Sir:

This communication is responsive to the non-final Office Action which was mailed from the U.S. Patent and Trademark Office on June 4, 2007 (Paper No. 20070503). A separate petition for the appropriate extension of time in which to respond is being filed concurrently herewith. Please amend the application as follows.

Amendments to the Claims are reflected in the listing of claims which begins on page 2 of this paper.

Remarks/Arguments begin on page 8 of this paper.

AMENDMENTS TO THE CLAIMS

1-141. (Canceled).

142. (Currently amended) An isolated antibody, or antigen-binding portion thereof, which is capable of binding to an epitope of the p40 subunit of IL-12, wherein the antibody is selected from the group consisting of a chimeric antibody, a humanized antibody and a human antibody .

143. (Previously presented) The antibody of claim 142, or antigen-binding portion thereof, which is capable of binding to the epitope of the p40 subunit when the p40 subunit is bound to the p35 subunit of IL-12.

144. (Previously presented) The antibody of claim 142, or antigen-binding portion thereof, which is capable of binding to the epitope of the p40 subunit when the p40 subunit is bound to a p19 subunit.

145. (Previously presented) The antibody of claim 142, or antigen-binding portion thereof, which is capable of binding to the epitope of the p40 subunit when the p40 subunit is bound to the p35 subunit of IL-12 and when the p40 subunit is bound to a p19 subunit.

146. (Previously presented) The isolated antibody of claim 142, or antigen binding portion thereof, wherein the antibody binds to an epitope of the p40 subunit of IL-12 to which an antibody selected from the group consisting of Y61 and J695 binds.

147. (Previously presented) The antibody of claim 142, wherein the antibody is further capable of binding to a first heterodimer and is also capable of binding to a second heterodimer, wherein the first heterodimer comprises the p40 subunit of Il-12 and the p35 subunit of Il-12, and wherein the second heterodimer comprises the p40 subunit of IL-12 and a p19 subunit.

148. (Currently amended) The antibody of claim 147, wherein the antibody neutralizes the biological activity of the first heterodimer.

149. (Currently amended) The antibody of claim 147, wherein the antibody neutralizes the biological activity of the second heterodimer.

150. (Currently amended) The antibody of claim 147, wherein the antibody neutralizes the biological activity of the first heterodimer and the second heterodimer.

151. (Previously presented) The isolated antibody of claim 148 or 150, or antigen binding portion thereof, which inhibits phytohemagglutinin blast proliferation in an *in vitro* PHA assay with an IC_{50} of 1×10^{-9} M or less, or which inhibits human IFNγ production with an IC_{50} of 1×10^{-10} M or less.

152. (Previously presented) The isolated antibody of any one of claims 142-145, or antigen binding portion thereof, which dissociates from the p40 subunit of IL-12 with a K_d of 1×10^{-10} M or less or a k_{off} rate constant of 1×10^{-3} s^{-1} or less, as determined by surface plasmon resonance.

153. (Previously presented) The isolated antibody of any one of claims 142-145, or antigen binding portion thereof, which is a chimeric antibody.

154. (Previously presented) The isolated antibody of any one of claims 142-145, or antigen binding portion thereof, which is a humanized antibody.

155. (Previously presented) The isolated antibody of any one of claims 142-145, or antigen binding portion thereof, which is a human antibody.

156. (Previously presented) The isolated antibody of claim 155, or antigen binding portion thereof, which has a heavy chain CDR3 comprising the amino acid sequence of SEQ ID NO: 25 and a light chain CDR3 comprising the amino acid sequence of SEQ ID NO: 26;

157. (Previously presented) The isolated antibody of claim 155, or antigen binding portion thereof, which has a heavy chain CDR2 comprising the amino acid sequence of SEQ ID NO: 27 and a light chain CDR2 comprising the amino acid sequence of SEQ ID NO: 28.

158. (Previously presented) The isolated antibody of claim 155, or antigen binding portion thereof, which has a heavy chain CDR1 comprising the amino acid sequence of SEQ ID NO: 29 and a light chain CDR1 comprising the amino acid sequence of SEQ ID NO: 30.

159. (Currently amended) An isolated antibody, or antigen-binding portion thereof, which is capable of binding to an interleukin comprising a p40 subunit, wherein the antibody is selected from the group consisting of a chimeric antibody, a humanized antibody and a human antibody.

160. (Previously presented) The antibody of claim 159, wherein the interleukin comprises a p40 subunit and a p35 subunit.

161. (Previously presented) The antibody of claim 160, wherein the interleukin is IL-12.

162. (Previously presented) The antibody of claim 159, wherein the interleukin comprises a p40 subunit and a p19 subunit.

163. (Previously presented) The isolated antibody of any one of claims 159-162, or antigen binding portion thereof, wherein the antibody binds to an epitope of the p40 subunit.

164. (Previously presented) The isolated antibody of any one of claims 159-162, or antigen binding portion thereof, wherein the antibody binds to an epitope of the p40 subunit to which an antibody selected from the group consisting of Y61 and J695 binds.

165. (Previously presented) The isolated antibody of claim 159, or antigen binding portion thereof, which dissociates from the p40 subunit of the interleukin with a K_d of 1×10^{-10}

expected to also neutralize both the p35/p40 molecules and the p19/p40 molecules." Based on these teachings in the specification, one of ordinary skill in the art would recognize that the "p19 subunit" recited in the claims refers to the p19 subunit of IL-23. Indeed, the Examiner explicitly states that ***"[t]he specification teaches one specific p19 subunit, which the Examiner recognizes is the p19 subunit of IL-23"*** (emphasis added). As clarified above for the record, ***Applicants' intention is to encompass only the p19 subunit of IL-23***, and not any other protein with a molecular weight of 19 kDa. Moreover, the Examiner specifically acknowledges that the specification is "***enabling for an isolated antibody... capable of binding p40 bound to the 19 subunit described in the instant specification***."

In view of the ample teachings provided in the specification, a person of ordinary skill in the art would be able to make and use the claimed antibodies using only routine experimentation. Accordingly, Applicants respectfully request that this rejection of the claims under 35 U.S.C. 112, first paragraph, for lack of enablement be reconsidered and withdrawn.

***Rejection of Claims* 142-145, 147-150, 159-163, 166 and 174**
Under 35 U.S.C. § 102(b)

Chizzonite *et al.*

The Examiner has rejected claims 142-145, 147-150, 159-163, 166 and 174 under 35 U.S.C. §102(b) as being anticipated by Chizzonite *et al.* ((1991) *J. Immunol.* Vol. 147:1548-1556). The Examiner relies on Chizzonite *et al.* for teaching "an antibody capable of binding the p40 subunit of IL-12 alone and in a heterodimer with IL-12 p35," and for teaching that "this antibody neutralizes activity of the IL-12 p40/p35 heterodimer." The Examiner acknowledges that "Chizzonite *et al.* does not specifically recite an antibody capable of binding IL-12 p40 bound to a p19 subunit." The Examiner alleges, however, that "it is known in the art that the cytokine IL-23 consists of the IL-12 subunit and a p19 subunit.... [t]herefore, it would be expected, in absence of evidence to the contrary, that the antibodies of Chizzonite *et al.* would inherently bind an IL-12 p40 subunit bound to an IL-23 p19 subunit, and neutralize activity of both an p40/035 heterodimer and ap40/p19 heterodimer." The Examiner concludes that "[b]ecause the USPTO does not have the facilities for testing the antibodies of Chizzonite *et al.*,

the burden is on the Applicants to show a novel and unobvious different between the claimed antibody and that of the prior art."

Applicants respectfully traverse this rejection on the grounds that Chizzonite *et al.* fail to teach or suggest each and every element of the claimed invention in accordance with 35 U.S.C. §102(b). Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

For a prior art reference to anticipate a claimed invention under 35 U.S.C. 102, the prior art must teach *each and every element* of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Claim 42, and claims 143-145,147-150 and 174 which depend therefrom, as currently amended, are directed to an isolated antibody, or antigen-binding portion thereof, which is capable of binding to an epitope of the p40 subunit of IL-12, ***wherein the antibody is selected from the group consisting of a chimeric antibody, a humanized antibody and a human antibody***. Claim 159, and claims 160-163, 166 and 174 which depend therefrom, as currently amended, are directed to an isolated antibody, or antigen-binding portion thereof, which is capable of binding to an interleukin comprising a p40 subunit, ***wherein the antibody is selected from the group consisting of a chimeric antibody, a humanized antibody and a human antibody***.

Applicants submit that the cited reference fails to teach each and every element of the present invention either explicitly or impliedly. In particular, Chizzonite *et al.* fails to teach an anti-p40 antibody as presently claimed. The pending claims are directed to an antibody, or antigen-binding portion thereof, that is capable of binding to an epitope of the p40 subunit of IL-12 or to an interleukin comprising a p40 subunit, where the antibody is either a ***chimeric*** antibody, ***humanized*** antibody or ***human*** antibody. In contrast, the teachings of Chizzonite *et al.* are directed solely to the production and identification of ***rat*** monoclonal antibodies that bind to the p40 subunit of IL-12. Chizzonite *et al.* fail to teach the production or identification of ***any*** antibodies specific for the p40 subunit of IL-12 other than rat antibodies, let alone a chimeric, humanized or human antibody. For the foregoing reasons, Chizzonite *et al.* fail to teach or suggest the claimed invention. Accordingly, Applicants respectfully request that the rejection of these claims as being anticipated by Chizzonite *et al.* be reconsidered and withdrawn.

D'Andrea *et al.*

The Examiner has also rejected claims 142-145, 147-150, 159-163, 166 and 174 under 35 U.S.C. §102(b) as being anticipated by D'Andrea *et al.* ((1992) *J. Exp. Med.* Vol. 176:1387-1398). The Examiner relies on D'Andrea *et al.* for teaching "antibodies capable of binding the p40 subunit of IL-12, alone and in a heterodimer with IL-12 p35," and for teaching that these antibodies "neutralize activity of the IL-12 p40/p35 heterodimer." The Examiner acknowledges that "D'Andrea *et al.* does not specifically recite an antibody capable of binding IL-12 p40 bound to a p19 subunit." The Examiner alleges, however, that "it is known in the art that the cytokine IL-23 consists of the IL-12 subunit and a p19 subunit." The Examiner further alleges that the antibodies taught by D'Andrea *et al.*, and specifically antibodies C8.6 and C11.5... have been shown to recognize IL12 p40 bound to a p19 subunit," citing Oppmann et al. ((2000) Immunity Vol. 13:715-725), the Parmingen catalog technical data sheet for product #554659 (antibody C8.6) and the Biolegend catalog description for product #501812 (antibody C11.5) in support of this allegation. The Examiner further concludes that, "in absence of evidence to the contrary, [the antibodies of D'Andrea *et al.*] would be expected to neutralize the activity of an p40/p19 heterodimer." The Examiner concludes that "[b]ecause the USPTO does not have the facilities for testing the antibodies of D'Andrea *et al.*, the burden is on the Applicants to show a novel and unobvious difference between the claimed antibody and that of the prior art."

Applicants respectfully traverse this rejection on the grounds that D'Andrea *et al.* fail to teach or suggest each and every element of the claimed invention in accordance with 35 U.S.C. §102(b). Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

For a prior art reference to anticipate a claimed invention under 35 U.S.C. 102, the prior art must teach *each and every element* of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Applicants submit that the cited reference fails to teach each and every element of the present invention either explicitly or impliedly. In particular, D'Andrea *et al.* fail to teach or suggest an anti-p40 antibody as presently claimed. As discussed above, the pending claims, as amended, are directed to an antibody, or antigen-binding portion thereof, that is capable of binding to an epitope of the p40 subunit of IL-12 or to an interleukin comprising a p40 subunit, where the antibody is either a ***chimeric*** antibody, ***humanized*** antibody or ***human*** antibody. In contrast, the teachings of D'Andrea *et al.* are directed solely to the production and identification

of ***mouse*** monoclonal antibodies that bind to the p40 subunit of IL-12. D'Andrea *et al.* fail to teach the production or identification of ***any*** antibodies specific for the p40 subunit of IL-12 other than ***mouse*** antibodies, let alone a chimeric, humanized or human antibody. For the foregoing reasons, D'Andrea *et al.* fail to teach or suggest the claimed invention. Accordingly, Applicants respectfully request that the rejection of these claims as being anticipated by D'Andrea *et al.* be reconsidered and withdrawn.

Wolf *et al.*

The Examiner has further rejected claims 142-145, 147-150, 159-163, 166 and 174 under 35 U.S.C. §102(b) as being anticipated by Wolf *et al.* ((1991) *J. Immunol.* Vol. 146:3074-3081). The Examiner relies on Wolf *et al.* for teaching "antibodies capable of binding the p40 subunit of IL-12, alone and in a heterodimer with IL-12 p35," and for teaching that these antibodies "neutralize activity of the IL-12 p40/p35 heterodimer." The Examiner acknowledges that "Wolf *et al.* does not specifically recite an antibody capable of binding IL-12 p40 bound to a p19 subunit." The Examiner alleges, however, that "it is known in the art that the cytokine IL-23 consists of the IL-12 subunit and a p19 subunit.... [t]herefore, it would be expected, in absence of evidence to the contrary, that the antibodies of Wolf *et al.* would inherently bind an IL-12 p40 subunit bound to an IL-23 p19 subunit, and neutralize activity of both an p40/035 heterodimer and ap40/p19 heterodimer." The Examiner concludes that "[b]ecause the USPTO does not have the facilities for testing the antibodies of Wolf *et al.*, the burden is on the Applicants to show a novel and unobvious difference between the claimed antibody and that of the prior art."

Applicants respectfully traverse this rejection on the grounds that Wofl *et al.* fail to teach or suggest each and every element of the claimed invention in accordance with 35 U.S.C. §102(b). Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

For a prior art reference to anticipate a claimed invention under 35 U.S.C. 102, the prior art must teach *each and every element* of the claimed invention. *Lewmar Marine v. Barient*, 827 F.2d 744, 3 USPQ2d 1766 (Fed. Cir. 1987).

Applicants submit that the cited reference fails to teach each and every element of the present invention either explicitly or impliedly. In particular, Wolf *et al.* fails to teach an anti-p40 antibody as presently claimed. As discussed above, the pending claims, as amended, are directed to an ***isolated antibody***, or antigen-binding portion thereof, that is capable of binding to

an epitope of the p40 subunit of IL-12 or to an interleukin comprising a p40 subunit, where the antibody is either a ***chimeric*** antibody, ***humanized*** antibody or ***human*** antibody. In contrast, Wolf *et al.* are directed solely to the production and identification of ***rabbit polyclonal*** antiserum containing antibodies that bind to the p40 subunit of IL-12. Wolf *et al.* fail to teach the production or identification of ***any*** monoclonal antibodies specific for the p40 subunit of IL-12, let alone a chimeric, humanized or human antibody. For the foregoing reasons, Wolf *et al.* fail to teach or suggest the claimed invention. Accordingly, Applicants respectfully request that the rejection of these claims as being anticipated by Wolf *et al.* be reconsidered and withdrawn.

Rejection of Claims 174-179 Under 35 U.S.C. § 103(a)

The Examiner has rejected claims 174-179 under 35 U.S.C. § 103(a) as being unpatentable over Chizzonite *et al.*, D'Andrea *et al.*, or Wolf *et al.*, in view of Ehrhardt *et al.* (U.S. 2002/0194631). The Examiner relies on Chizzonite *et al.*, D'Andrea *et al.* and Wolf *et al.* for the reasons set forth above. The Examiner further relies on Ehrhardt *et al.* for teaching "methods of treating psoriasis with anti-IL-12 antibodies, and specifically teaches administration of anti-IL-12 antibodies and additional agents, including methotrexate." In particular, the Examiner is of the opinion that "it would have been obvious to one of ordinary skill in the art, at the time the invention was conceived, to prepare a pharmaceutical composition comprising the antibodies taught by Chizzonite *et al.*, D'Andrea *et al.* and Wolf *et al.*... in a pharmaceutical composition further comprised of methotrexate." The Examiner alleges that the "motivation to do so comes from the teaching of Ehrhardt *et al.*, which teaches that both anti-IL-12 antibodies and methotrexate are useful for treatment of psoriasis."

Applicants respectfully traverse the Examiner's assertion that the claimed invention would have been obvious to the skilled artisan at the time it was made. Reconsideration and withdrawal of the rejection in light of the following discussion is respectfully requested.

To establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art reference must teach or suggest all the claim limitations. The teaching or suggestion to make the claimed combination and the reasonable expectation of success must be found in the prior art and not based on applicant's disclosure. *In re Vaeck*, 947 F.2d 488 (Fed. Cir. 1991). MPEP 706.02(j).